

Exhibit A

# FIELDS VIROLOGY

Third Edition

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FIG. 15. Family Birnaviridae, genus Birnavirus, infectious bursal disease virus (x189,000).

RNA, 5.7–5.9 kbp in overall size (infectious pancreatic necrosis virus: A segment 3,092 bp; B segment 2,784 bp). Both genome segments contain a 5'-genome-linked protein (VPg). There are no poly (A) tracts at the 3'-ends of the RNA segments. Virions contain five proteins: VP1 (Mr 94,000), the RNA-dependent RNA polymerase; pre-VP2 (Mr 62,000) and VP2 (Mr 54,000), the major capsid proteins; VP3 (Mr 30,000), an internal capsid protein; and VPg (Mr 94,000), the genome-linked protein. Infected cells also contain NS or VP4 (Mr 29,000), a virus-coded protease, and a positively charged minor protein (Mr 17,000). Virions contain no lipid. The VP2 capsid protein may be glycosylated. Replication involves the synthesis by the virion RNA-dependent RNA polymerase of two genome length mRNAs, one from each of the genome segments. Virus RNA is transcribed by a semi-conservative strand displacement mechanism. Segment A mRNA is translated to a Mr 10<sup>6</sup> polyprotein that is cleaved to form (5' to 3') the pre-VP2, VP4, and VP3 proteins. Pre-VP2 is later processed by a slow maturation cleavage to produce VP2. The mRNA from segment B is translated to form VP1. Virus particles assemble and accumulate in the cytoplasm. Natural hosts include salmonid fish, other freshwater and marine fishes, bivalve mollusks, chickens, ducks, turkeys, and other domestic fowl. The viruses are transmitted both vertically and horizontally; geographic distribution is worldwide. The viruses are sensitive to acid, heat, detergents, organic solvents, and UV- and  $\gamma$ -irradiation.

#### Human Pathogens

Genus *Birnavirus*: none known.

#### Animal Pathogens

Genus *Birnavirus*: infectious bursal disease virus of chickens, ducks, and turkeys; infectious pancreatic necrosis virus of fish.

### The Family Retroviridae

Family: *Retroviridae* (the retroviruses)

Genus: unnamed, mammalian type B retroviruses

Genus: unnamed, mammalian and reptilian type C retroviruses

Genus: unnamed, avian type C retroviruses

Genus: unnamed, type D retroviruses

Genus: unnamed, HTLV/BLV viruses

Genus: *Lentivirus* (lentiviruses) (Fig. 16)

Genus: *Spumavirus* (spumaviruses)

#### Characteristics (28,36,132)

Virions are spherical, enveloped, and 80–100 nm in diameter; they consist of a lipid-containing envelope, with peplomers 8 nm in length, surrounding an icosahedral capsid, which in turn contains a helical nucleocapsid. The nucleocapsid is eccentric in type B virions, concentric in type C, HTLV/BLV, and spumavirus virions, and rod or cone shaped in lentivirus virions. Virion buoyant density is 1.16–1.18 g/cm<sup>3</sup> in sucrose. The genome consists of a homodimer of linear, positive-sense, single-stranded RNA; each monomer is 7–11 kb in size. The monomers are held together noncovalently by hydrogen bonds and have a 3'-poly (A) tract, with a 5'-cap structure (type 1). Most of the viruses have four main genes coding for the virion proteins in the order 5'-*gag*, *pro*, *pol*, *env*-3'. Many of the viruses contain other genes encoding nonstructural proteins important for the regulation of gene expression.



FIG. 16. Family Retroviridae, genus Lentivirus, human immunodeficiency virus 1, displaying a typical conical core (top left x104,000); human immunodeficiency virus 1, immature virions displaying structured protein layer beneath the envelope (top right x104,000); simian immunodeficiency virus displaying triangular peplomers (bottom left x126,000); unnamed genus (mammalian type B retroviruses), mouse mammary tumor virus, displaying closely spaced peplomers (bottom right x112,000).

and virus replication; others carry (as inserts or as substitutions) cell-derived sequences that are important in pathogenesis. Virion proteins include two envelope proteins encoded by the viral *env* gene, three to six internal nonglycosylated structural proteins encoded by the *gag* gene, and, in order from the amino terminus, a matrix, capsid, and nucleocapsid protein. Other proteins are a protease encoded by the *pro* gene and a reverse transcriptase and integrase encoded by the *pol* gene. Virions contain lipids derived from the plasma membrane of the host cell. Virions contain carbohydrates as glycosylated envelope surface proteins. RNA replication is unique: replication starts with reverse transcription of virion RNA into cDNA. cDNA synthesis involves the concomitant digestion of the viral RNA (RNase of the reverse transcriptase) with the products of this digestion serving to prime positive-sense cDNA synthesis on the negative-sense DNA transcripts. In final form, the linear double-stranded DNA transcripts derived from the viral genome contain long terminal repeats; this DNA is circularized, integrated into the host chromosomal DNA, and then used for transcription, including transcription of full-length genomic RNA species. There are several classes of mRNA varying with the virus. An mRNA comprising the whole genome is a template for the translation of the *gag*, *pro*, and *pol* genes; translation yields polyprotein precursors that are cleaved to yield the structural proteins, protease, reverse transcriptase, and integrase. Virion assembly occurs via budding on plasma membranes. The viruses are widely distributed in vertebrates; endogenous proviruses (products of ancient infections of germ line cells, inherited as Mendelian genes) also occur widely in vertebrates. The viruses are associated with many different diseases, including leukemias, lymphomas, sarcomas, carcinomas, immunodeficiencies, autoimmune diseases, lower motor neuron diseases, and several acute diseases involving tissue damage. Virions are sensitive to heat, detergents, and formaldehyde, but relatively resistant to UV light.

#### Human Pathogens

Genus (unnamed, HTLV/BLV viruses): human T-cell lymphotropic viruses 1 and 2. Genus *Lentivirus*: human immunodeficiency viruses 1 and 2.

#### Animal Pathogens

Genus (unnamed, mammalian type B retroviruses): mouse mammary tumor virus. Genus (unnamed, mammalian and reptilian type C retroviruses): many murine leukemia viruses (e.g., Abelson, AKR (endogenous), Friend, Moloney murine leukemia viruses); many murine sarcoma viruses (e.g., Harvey, Kirsten, Moloney, Finkel-Biskis-Jenkins murine sarcoma viruses); feline leukemia virus; fe-

line sarcoma viruses; gibbon ape leukemia virus; woolly monkey sarcoma virus; porcine type C virus; guinea pig type C virus; and viper type C virus. Genus (unnamed, avian type C retroviruses): Rous sarcoma virus; avian carcinoma viruses; avian sarcoma viruses; avian leukosis viruses; avian myeloblastosis viruses; avian reticuloendotheliosis viruses; and duck spleen necrosis virus. Genus (unnamed, type D retroviruses): Mason-Pfizer monkey virus; simian type D virus 1; Langur type D virus; squirrel monkey type D virus; and ovine pulmonary adenocarcinoma virus (Jaagsiekte). Genus (unnamed, HTLV/BLV viruses): simian T-cell lymphotropic viruses; bovine leukemia virus. Genus *Lentivirus*: simian immunodeficiency viruses (African green monkey, sooty mangabey, stump-tailed macaque, pig-tailed macaque, Rhesus, chimpanzee, and mandrill viruses); visna/maedi virus; caprine arthritis-encephalitis virus; equine infectious anemia virus; feline immunodeficiency virus; and bovine immunodeficiency virus.

#### The Family Hepadnaviridae

Family: *Hepadnaviridae* (the hepadnaviruses) (Fig. 17)  
Genus: *Orthohepadnavirus* (hepadnaviruses of mammals)  
Genus: *Avihepadnavirus* (hepadnaviruses of birds)

#### Characteristics (50,59,65)

Virions are spherical and occasionally pleomorphic, 40–48 nm in diameter, with no evident surface projections. The envelope contains the surface antigens (HBsAg) and surrounds an icosahedral, 27–35 nm diameter nucleocapsid core constructed from 180 capsomers (core antigen, HBcAg) arranged in T = 3 symmetry. Buoyant density is 1.25 g/cm<sup>3</sup> in CsCl. The genome consists of a single molecule of DNA, which is circular (maintained by base-pairing of cohesive ends), nicked, and mainly



FIG. 17. Family *Hepadnaviridae*, genus *Hepadnavirus*, hepatitis B virus (×175,000).

four early, two intermediate, and one major late promoter. All primary transcripts are capped and polyadenylated. There are complex splicing patterns to produce families of mRNAs. Virions are assembled in the nucleus, often in paracrystalline arrays, and are released by cell destruction. Most viruses have a narrow host range. Experimentally, several of the viruses cause tumors in newborns of heterologous species. The viruses are stable under mild acidic conditions and are insensitive to lipid solvents.

### Human Pathogens

Genus: *Mastadenovirus*: human adenoviruses 1-49.

### Animal Pathogens

Genus *Mastadenovirus*: simian adenoviruses 1-27; bovine adenoviruses 1-9; porcine adenoviruses 1-4; ovine adenoviruses 1-6; equine adenoviruses 1 and 2; infectious canine hepatitis virus (canine adenovirus 1); canine adenovirus 2; caprine adenovirus 1; and murine adenoviruses 1 and 2. Genus *Aviadenovirus*: fowl adenoviruses 1-12; turkey adenoviruses 1-3; goose adenoviruses 1-3; pheasant adenovirus 1; and duck adenoviruses 1 and 2.

### The Family *Herpesviridae*

Family: *Herpesviridae* (the herpesviruses)

Subfamily: *Alphaherpesvirinae* (the herpes simplex-like viruses)

Genus: *Simplexvirus* (simplexviruses) (Fig. 22)

Genus: *Varicellovirus* (varicelloviruses)

Subfamily: *Betaherpesvirinae* (the cytomegaloviruses)

Genus: *Cytomegalovirus* (cytomegaloviruses)

Genus: *Muromegalovirus* (murine cytomegaloviruses)

Genus: *Roseolovirus* (human herpesvirus 6)

Subfamily: *Gammaherpesvirinae* (the lymphocyte-associated herpesviruses)

Genus: *Lymphocryptovirus* (Epstein-Barr-like viruses)

Genus: *Rhadinovirus* (saimiri-atelous-like herpesviruses)

### Characteristics (109,110)

Virions are spherical or pleomorphic, have an overall diameter of 150-200 nm, and consist of (a) an envelope with surface projections, (b) a tegument consisting of amorphous material, (c) an icosahedral nucleocapsid 100 nm in diameter with 162 (150 hexameric, 12 pentameric) prismatic capsomeres, and (d) a core consisting of a fibrillar spool on which the DNA is wrapped. Virion buoyant density is 1.20-1.29 g/cm<sup>3</sup> in CsCl. The genome consists of a



FIG. 22. Family *Herpesviridae*, genus *Simplexvirus*, human herpesvirus 1 (herpes simplex virus 1), enveloped (left), and naked capsids (right) ( $\times 147,000$ ).

single molecule of linear, double-stranded DNA 124-235 kbp in size. Genomic DNA sometimes contains terminal and internal reiterated sequences, sometimes forming two covalently linked components (L and S) that result in the formation of two or four isomeric forms oriented differently in the various subfamilies and genera. The viruses have been divided into six groups depending on the presence or absence and arrangement of the reiterated sequences. Virions have more than 30 structural proteins, and at least as many nonstructural proteins. Among the proteins specified by all herpesviruses are a DNA polymerase, DNA binding proteins, and a protease; there are many additional proteins with enzymatic activities, including as many as three protein kinases. Human herpesvirus 1 (herpes simplex virus 1) contains 11 glycosylated and at least two nonglycosylated proteins in its envelope, including an Fc receptor. Virions contain lipids, their composition matching host cell nuclear or other membranes. Carbohydrates associated with the viral envelope glycoproteins are of the complex high mannose type. Replication starts with circularization of viral DNA; transcription and translation are coordinately regulated and sequentially ordered in a cascade with three major stages. Immediate early genes are transcribed by nuclear enzymes, and mRNAs are transported to the cytoplasm and translated; proteins are then transported to the nucleus and are involved in the synthesis of additional mRNAs. Early proteins are involved in the replication of the viral DNA by a rolling circle mechanism. Late mRNAs are translated mostly into the structural proteins. Replication takes place in the nucleus, and capsids acquire their envelopes via budding through the inner lamella of the nuclear envelope. Virions are released via transport across the cytoplasm in membranous vesicles, which then fuse with the plasma membrane. The viruses generally have narrow host ranges. Transmission is usually by contact (infected cells in saliva, urogenital excretions, or free virus in aerosols). Some viruses induce neoplasia and most persist for the lifetime of their host. The viruses are sensitive to acid, heat, detergents, organic solvents, and UV- and  $\gamma$ -irradiation.

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**Human Pathogens**

Subfamily *Alphaherpesvirinae*/Genus *Simplexvirus*: human herpesviruses 1 and 2 (herpes simplex viruses 1 and 2); herpesvirus B (cercopithecine herpesvirus 1). Genus *Varicellovirus*: human herpesvirus 3 (varicella-zoster virus). Subfamily *Betaherpesvirinae*/Genus *Cytomegalovirus*: human herpesvirus 5 (human cytomegalovirus). Genus *Roseolovirus*: human herpesviruses 6A, 6B, and 7. Subfamily *Gammaherpesvirinae*/Genus *Lymphocryptovirus*: human herpesvirus 4 (Epstein-Barr virus).

**Animal Pathogens**

Subfamily *Alphaherpesvirinae*/Genus *Simplexvirus*: herpesvirus B (cercopithecine herpesvirus 1); bovine herpesvirus 2 (bovine mamillitis virus, pseudo-lumpy skin disease virus). Genus *Varicellovirus*: equid herpesvirus 1 (equine abortion virus); equid herpesvirus 4 (equine rhinopneumonitis virus); bovine herpesvirus 1 (infectious bovine rhinotracheitis virus); and pseudorabies virus (suid herpesvirus 1, Aujeszky's disease virus). Unclassified in the Subfamily: many simian herpesviruses [ateline herpesvirus 1 (spider monkey herpesvirus); cercopithecine herpesviruses 2 (SA2), 6, 7, and 9; saimiriine herpesvirus 1 (marmoset herpesvirus)]; equid herpesvirus 3 (equine coital exanthema virus); asinine herpesviruses 1 and 3; bovine herpesvirus 5 (bovine encephalitis herpesvirus); canid herpesvirus 1 (canine herpesvirus); caprine herpesvirus 1 (goat herpesvirus); cervid herpesviruses 1 and 2; felid herpesvirus 1 (feline rhinotracheitis virus); gallid herpesvirus 1 (infectious laryngotracheitis virus); and anatid herpesvirus 1 (duck plague herpesvirus). Subfamily *Betaherpesvirinae*/Genus *Muromegalovirus*: mouse cytomegalovirus 1. Unclassified in the Subfamily: many simian/primates herpesviruses [aotine herpesviruses 1 and 3 (aotus cytomegaloviruses 1 and 3); callitrichine herpesvirus 2 (marmoset cytomegalovirus 2); pongine herpesviruses 1, 2, and 3 (chimpanzee, orangutan, and gorilla herpesviruses); cebine herpesviruses 1 and 2 (capuchin herpesviruses); cercopithecine herpesviruses 3, 4, 5, and 8 (simian cytomegaloviruses); cercopithecine herpesvirus 12 (baboon herpesvirus)]; equid herpesviruses 2 and 5 (equine cytomegaloviruses); suid herpesvirus 2 (swine cytomegalovirus, inclusion-body rhinitis virus); caviid herpesvirus 2 (guinea pig cytomegalovirus); murid herpesvirus 2 (rat cytomegalovirus). Subfamily *Gammaherpesvirinae*/Unclassified in the Subfamily: alcelaphine herpesvirus 1 (malignant catarrhal fever virus of cattle, wildebeest herpesvirus); ovine herpesvirus 2 (sheep-associated malignant catarrhal fever of cattle herpesvirus); bovine herpesvirus 4 (Moor herpesvirus); equid herpesviruses 2 and 5; caviid herpesvirus 1 (guinea pig herpesvirus 1); and herpesvirus saimiri 2 (saimiriine herpesvirus 2, squirrel monkey herpesvirus). Unclassified in the Family: many herpesviruses of rodents; channel catfish herpesvirus and other her-

pesviruses of fish; chelonid herpesvirus 1 (gray patch disease agent of green sea turtle) and other herpesviruses of turtles, lizards, and amphibians; several herpesviruses of snakes; gallid herpesviruses 2 and 3 (Marek's disease viruses); and psittacid herpesvirus 1 (parrot herpesvirus, Pacheco's disease) and many herpesviruses of other birds.

**The Family *Poxviridae***

Family: *Poxviridae* (the poxviruses) (Fig. 23)

Subfamily: *Chordapoxvirinae* (the poxviruses of vertebrates)

Genus: *Orthopoxvirus* (orthopoxviruses)

Genus: *Parapoxvirus* (parapoxviruses)

Genus: *Avipoxvirus* (fowlpoxviruses)

Genus: *Capripoxvirus* (sheeppoxlike viruses)

Genus: *Leporipoxvirus* (myxomaviruses)

Genus: *Suipoxvirus* (swinepoxviruses)

Genus: *Molluscipoxvirus* (molluscum contagiosum viruses)

Genus: *Yatapoxvirus* (yabapox and tanapox viruses)

Subfamily: *Entomopoxvirinae* (the poxviruses of insects)

Genus: *Entomopoxvirus A* (insect poxvirus group A)

Genus: *Entomopoxvirus B* (insect poxvirus group B)

Genus: *Entomopoxvirus C* (insect poxvirus group C)

**Characteristics (40,46,47)**

Virions are large and brick shaped, 220–450 nm long × 140–260 nm wide × 140–260 nm thick (or ovoid in the case of the genus *Parapoxvirus*, 250–300 nm long × 160–190 nm wide), and consist of (a) an external envelope derived from the cell but containing virus-specified proteins, (b) a complex coat of regular spiral filaments 10–20 nm in diameter, and (c) an internal biconcave or cylindrical core that contains the genome DNA and proteins organized in a nucleoprotein complex and one or two lateral bodies. Virion buoyant density is 1.16 g/cm<sup>3</sup> in sucrose and 1.25 g/cm<sup>3</sup> in CsCl. The genome consists of a single molecule of linear, covalently closed, double-stranded DNA



FIG. 23. Family *Poxviridae*, genus *Orthopoxvirus*, vaccinia virus (left) (×20,900); genus *Parapoxvirus*, ort virus (right) (×33,000).



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